

REMARKS/ARGUMENTS

Claims 7-11 and 13-16 were pending; Claims 1-6 and 12 are canceled. Claim 16 is withdrawn from consideration. Claim 7 is amended. No new matter is added. Support for the amending language of Claim 7 may be found in originally filed Claim 3. No new matter is added by the amendment as it is based on an original claim. Entry of the amendment is requested. Reconsideration of the rejections is requested.

Paragraph 85 is amended herewith to include a sequence identifier. A substitute Seqlist is attached herewith. Withdrawal of the objection is requested.

Claim 7 has been rejected under 35 U.S.C. 102(e) as anticipated by Rodan *et al.*, U.S. Patent no. 5,780,291. Applicants respectfully submit that the cited art fails to teach a method of isolating a biologically active, substantially homogeneous composition of Wnt protein comprising a lipid moiety.

Applicants respectfully submit that the cited art does not teach the presently claimed methods. It may be noted that the cited document is silent as to the hydrophobic nature of Wnt proteins, and to the presence of a lipid moiety.

The Office Action states that "The Examiner does not question the activity of the Rodan *et al.* protein because it is reasonably presumed from the patent that the techniques used were sufficient for the isolation and purification of the Wnt protein." Applicants respectfully submit that such a presumption is rebutted by the attached Declaration. As discussed in the attached Declaration under 37 C.F.R. 1.132 by Dr. Karl Willerts, the methods described in the '291 patent do not teach one of skill in the art how to isolate a substantially homogeneous, biologically active Wnt protein, where the protein comprises a lipid moiety. It is further noted by Applicants, with respect to the teachings of the '291 patent, that no evidence is provided in the patent as to any biological activity or purity of Wnt protein compositions.

The Office Action states that "The Examiner will note that all issued patents are presumed enabled and sufficiently described, among other things that do not apply instantly." Applicants respectfully submit that the law under 35 U.S.C. § 282 states "A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims." It is the claimed subject matter that is presumed to be valid, (and thus enabled) not the teachings of the specification.

The pertinent claim of the '291 patent reads as follows:

1. An isolated and purified Wnt-x protein wherein said protein is characterized by the amino acid sequence:

MLRPGGAEEAAQLPLRRASAPVPVPSAAPDGSRASA
RLGLACLILLLLLLTLPARVDTSWWYIGALGARVICDN
IPGLVSRQRQLCQRYPDIMRSVGEAREWIRECQHOF
RHHRWNCITLDRDHTVFGRVMLRSSRDGAFVYAIS
AGVVHAITRACSQGELSVCSDDPYTRGRHHIDQRGDF
DWGGCSDNHYGVRFKAFVDAKEKRLKDARALMN
LHNRCCKRTVSTHVCARRFLKLECKCHGVSGSCTL
RTCWRALSDFRRTGDYLRRRTDGAQVMATQDGAN
FTAARQGYRRATRTDLVYLTPADYCVLDKAAGSLG
TAGRVCSKTSKGTGDCCEMCCGRGYDTRVTRVTQC
ECKFWCCAVRCKECRNTVDVHTCKAPIKKAEWLDQ
T [SEQ.ID.NO.: 8]

The claim of the '291 patent does not speak of a biologically active Wnt protein; does not speak of a Wnt protein comprising a lipid moiety; and does not speak of a substantially homogeneous composition of such a Wnt protein. Thus, that portion of the '291 patent which is presumed to be valid (i.e. the claimed subject matter) fails to teach multiple important characteristics of Applicants claimed invention. The limitations of instant Claim 7 are not met by Rodan *et al.*

Applicants respectfully submit that Claim 7 is not anticipated by the teachings of the cited art, in view of the above amendments and remarks, and the attached Declaration. Withdrawal of the rejection is requested.

Claims 7-15 have been rejected under 35 U.S.C. 103 as made obvious by the combination of Rodan *et al.*, U.S. 5,780,291 in further view of Lambeth *et al.*, U.S. 6,620,603, Vernet *et al.*, U.S. 6,653,448; and Matthews *et al.*, U.S. 6,159,462. Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references.

The Office Action states that "the methods of Rodan *et al.* are considered patentable by weight and therefore the rationale of Rodan *et al.* in conjunction with Lambeth *et al.* and Matthews *et al.* is maintained."

Applicants respectfully submit that the methods of Rodan *et al.* are not presumed valid, as discussed above, only the composition as set forth in Claim 1 of the '291 patent is entitled to a presumption of validity. This claim does not teach the isolation of a substantially homogeneous, biologically active Wnt protein, where the protein comprises a lipid moiety, for the reasons discussed above and set forth in the attached Declaration.

The Office Action states that "Applicant has not removed the nexus between the prior art references by attacking the validity of the Rodan *et al.* patent". Applicants respectfully submit that the rejection made under 35 U.S.C. 103 is based on Rodan *et al.*, in view of the secondary references. As discussed above, it is Applicants' position that Rodan *et al.* fails to teach the instantly claimed methods. The presumed validity of the Rodan *et al.* patent is not under discussion, because the patent does not claim methods of isolating a Wnt protein comprising a lipid moiety to produce a biologically active, substantially homogeneous composition.

The secondary references also fail to teach a method of isolating a Wnt protein comprising a lipid moiety to produce a biologically active, substantially homogeneous composition. As noted by the Examiner, Lambeth *et al.* does not teach Wnt peptides, and therefore does not teach the specific application of peptides to the isolation of Wnt proteins.

The cited passage of Matthews *et al.* reads as follows:

6. Purification of Wnt Polypeptide

Wnt polypeptide may be recovered from the culture medium as a secreted polypeptide, although it is preferentially recovered from host cell lysates. If the Wnt polypeptide is membrane-bound, it can be released from the cell surface using suitable agents, including enzymes or detergents (e.g. Triton®X-100), for example, suramin, PMA, heparin, Heparinase I and III, plasmin, n-Octyl-beta-D-glucoside, PI-specific- and PC-specific-phospholipase C and TNF-alpha.

When Wnt polypeptide is produced in a recombinant cell other than one of human origin, the Wnt polypeptide is completely free of proteins or polypeptides of human origin. However, it is necessary to purify Wnt polypeptide from recombinant cell proteins or polypeptides to obtain preparations that are substantially homogeneous as to Wnt polypeptide. As a first step, the culture medium or lysate is centrifuged to remove particulate cell debris. Wnt polypeptide thereafter is purified from contaminant soluble proteins and polypeptides, with the following procedures being exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex®G-75; and protein A Sepharose™ columns to remove contaminants such as IgG.

While the passage refers to the use of detergents to release the Wnt polypeptide from the cell, it does not teach the isolation of the Wnt protein in a concentration of detergent sufficient to

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maintain solubility of the protein, nor does it teach a substantially homogeneous composition of biologically active Wnt protein.

As discussed at length in Applicants' previous response, other publications by Matthews illustrate the difficulty of Wnt purification, in that Matthews dialyzed the protein against PBS, thereby failing to retain activity during purification.

The secondary references fail to remedy the deficiencies of the primary reference. While various methods of isolating proteins are known in the art, until Applicants' determination that Wnt comprises an unexpected lipid moiety, there was no motivation to isolate Wnt in a manner that would preserve its activity. As discussed in Applicants' previous response, the prior art taught approaches to purification of Wnt proteins, but not their successful conclusion. Regardless of the motivation provided Lambeth *et al.* and Matthews *et al.*, the guidance for successful practice of the instantly claimed invention was not available prior to the teachings of the instant application.

In view of the above amendments, Declaration, and remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 103. Withdrawal of the rejection is requested.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-299.

Respectfully submitted,
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